# Alkaloids from *Ochrosia borbonica*

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Ten new monoterpenoid indole alkaloids, ochroborines A and B (**1** and **2**, resp.), 10-hydroxyisovallesiachotamine (**3**), 10-hydroxyisositsirikine (**4**), 10,11-dimethoxysitsirikine (**5**), 10-methoxyapoyohimbine (**6**), 10-hydroxyakuammidine (**7**), akuammidine 17-*O*-$\beta$-D-glucoside (**8**), 15$\alpha$-hydroxyapparicine (**9**), and 15$\alpha$-hydroxy-10-methoxyapparicine (**10**), and 24 known alkaloids were isolated from leaves and twigs of *Ochrosia borbonica* J. F.GMEL. These structures were elucidated based on 1D- and 2D-NMR, FT-IR, UV, and MS data. 10-Hydroxyisovallesiachotamine (**3**), ellipticine, and 10-methoxyellipticine showed cytotoxic activities against five human cancer cell lines.

**Introduction.** – Plants of the genus *Ochrosia* JUSS., family Apocynaceae, are trees naturally distributed in tropical or subtropical Malaysia, and west of Pacific Islands, and three species of the genus are cultivated in Guangdong and Taiwan Provinces [1]. This genus, as a good source of monoterpenoid indole alkaloids (MIAs) [2], especially the ellipticine derivatives with the anticancer activities, has attracted pharmacologists' attentions [3]. As a continuation of our studies on bioactive MIAs, we investigated chemical constituents of *O. borbonica* J.F.GMEL. since the species cultivated in Guangdong Province, China, was not reported regarding its alkaloid contents. Herein, we describe the isolation, structure determination, and cytotoxic activities of ten new alkaloids **1**–**10** (*Fig. 1*), together with those of the 24 known alkaloids, namely, reserpiline, isoreserpiline pseudoindoxyl, ellipticine, epchrosine, 10-methoxyellipticine, 11-methoxyapoyohimbine, 10,11-dimethoxypicraphylline, akuammidine, 11-methoxypseudoyohimbine, 10-methoxyapparicine, 11-methoxy-$\beta$-yohimbine, hervine, 16-epiisositsirikine, 16-epipleiocarpamine, (16*R*)-10-methoxyisositsirikine, (16*S*)-10-methoxyisositsirikine, carapanaubine, 3-epicarapanaubine, 18,19-dihydro-10-methoxysitsirikine, cabucine, ochropposine, isovallesiachotamine, begonanline, and apparicine.

**Results and Discussion.** – The MeOH extract of *O. borbonica* leaves and twigs was partitioned between $H_2O$ and AcOEt after acid–base treating, and column chromatography over silica, and $C_{18}$ silica was used to separate the alkaloidal fraction into 34 alkaloids.

Alkaloid **1** had the molecular formula of $C_{23}H_{26}N_2O_6$, indicated by HR-ESI-MS (*m*/*z* 427.1870 ($[M+H]^+$)), in combination with $^1$H- and $^{13}$C-NMR, and DEPT spectra. Maximal absorptions at 232 and 292 nm in the UV spectrum of **1** were identical to those

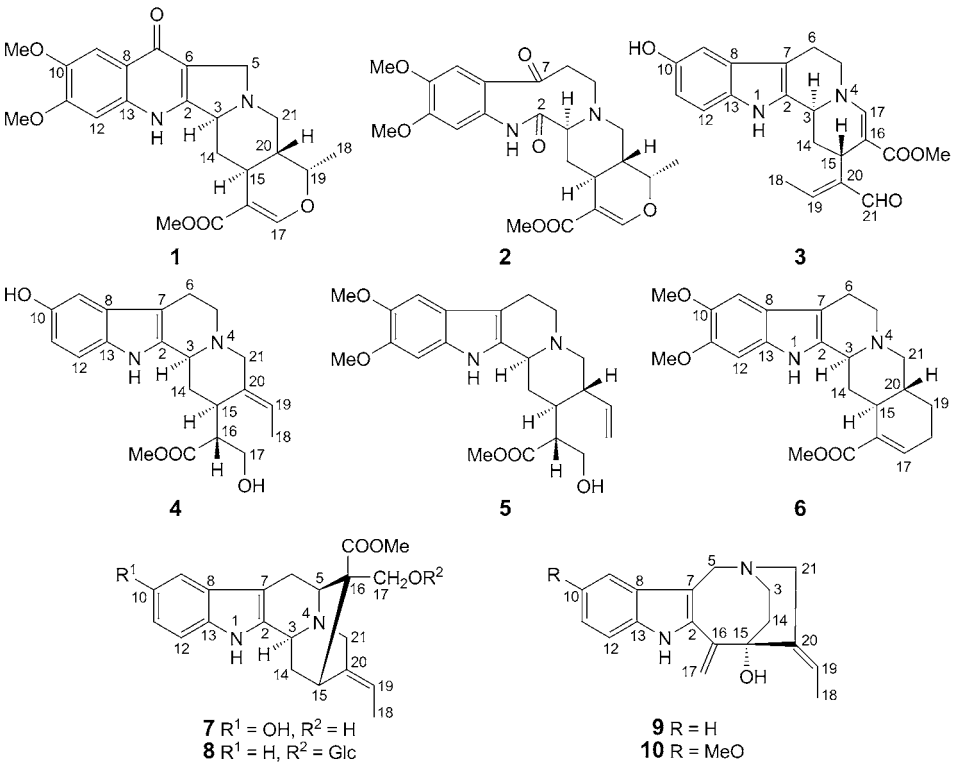


Fig. 1. *New alkaloids* **1**–**10** *isolated from* O. borbonica

of meloyunine C [4], showing a conjugating group. Its IR spectrum indicated the presence of NH (3433 $cm^{-1}$) and C=O (1705 $cm^{-1}$) groups, and of a benzene ring (1623 $cm^{-1}$). Additionally, in the $^{13}$C-NMR spectrum of **1**, the signal corresponding to a conjugated C=O group at $\delta$(C) 173.0 (*s*, C(7)), together with signals at $\delta$(C) 154.1 (*s*, C(2)) and 116.8 (*s*, C(6)) confirmed that **1** contained a quinolone rather than an indole moiety (*Table 1*) [4]. In the HMBC spectrum of **1**, the H-atom signal at $\delta$(H) 7.62 (*s*) correlating with that of C(7) was placed at C(9), and the signal at $\delta$(H) 7.51 (*s*) correlating with that at $\delta$(C) 121.0 (*s*, C(8)) was assigned to C(12). Further, C-atom signals at $\delta$(C) 155.9 (*s*) and 148.2 (*s*) were correlated with the above H-atom signals and with that of the MeO group in the HMBC spectrum, suggesting that **1** was a 10,11-dimethyl disubstituted quinolone (*Fig. 1*). The remaining C-atom signal pattern was similar to that of reserpilline [5]. The $^{1}$H- (*Table 2*) and $^{13}$C-NMR spectra were assigned by the HSQC and HMBC experiments, and the configurations at C(3), C(14), C(15), and C(18) were assigned to be as in the core of reserpilline by biogenetic reasons and confirmed through the ROESY correlations (*Fig. 2*).

The HR-ESI-MS (*m*/*z* 467.1794 ($[M + Na]^+$)) of **2** provided the molecular formula $C_{23}H_{28}N_2O_7$. The downfield $^{13}$C-NMR signals ($\delta$(C) 199.2 (C(7)) and 174.4 (C(2))) indicated that **2** was similar to melohenine B [6], while the remaining $^{13}$C resonances ($\delta$(C) 167.6, 155.6, 153.4, 149.0, 110.7), especially the upfield $^{13}$C signals ($\delta$(C) 73.2 (*d*),

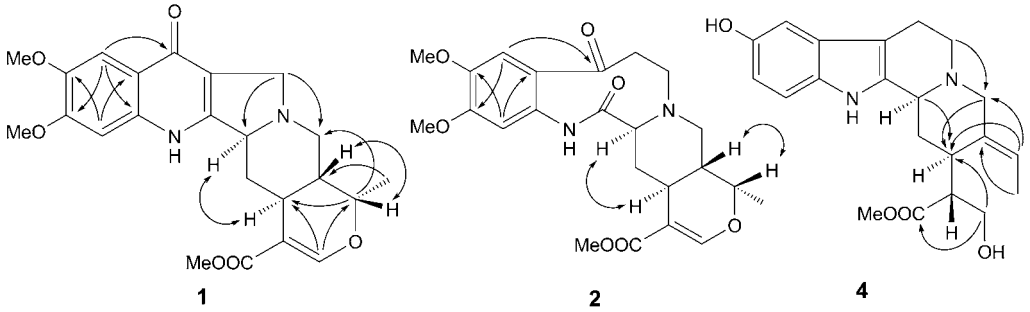


Fig. 2. *Key HMB* (H → C) *and ROESY* (H ↔ H) *correlations of* **1**, **2**, *and* **4**

72.5 (*d*), 56.8 (*t*), 38.6 (*d*), 30.4 (*d*), 33.0 (*t*), and 18.3 (*q*)) were similar to those of **1**. So, **2** was a dioxo 'intermediate' between reserpilline and compound **1**, and named ochroborine B. The structure elucidation of **2** was further supported by the HMBC spectrum (*Fig. 2*), establishing another monoterpenoid quinoline alkaloid derived from indole [4].

Alkaloid **3** was found to possess the molecular formula $C_{21}H_{22}N_2O_4$, deduced from HR-ESI-MS (*m/z* 367.1660 ($[M + H]^+$)), implying twelve degrees of unsaturation. UV Maxima at 229, 282, and 292 nm evidenced the presence of an indole ring and an $\alpha,\beta$-unsaturated keto group. The IR spectrum indicated the presence of NH (3432 $cm^{-1}$), C=O (1722 $cm^{-1}$), and olefin groups (1628 $cm^{-1}$). The $^1$H- and DEPT-NMR spectrum showed signals of a mono-substituted indole ring ($\delta$(H) 6.69 (*s*, H–C(9)), 6.54 (*d*, $J$ = 7.5, H–C(11)), 7.05 (*d*, $J$ = 7.5, H–C(12)), 10.59 (*s*, H–N(1))). The upfield CHO (($\delta$(C) 195.7 (*d*) and $\delta$(H) 9.33 (*s*)), MeOCO signals ($\delta$(C) 167.2 (*s*), 50.2 (*q*)), and two downfield C=C bond H-atom signals ($\delta$(H) 7.67 (*s*) and 6.74 (*q*, $J$ = 7.5, 1 H)) further revealed the presence of two $\alpha,\beta$-unsaturated ester and CHO groups [7], confirmed by HMBCs of the signal at $\delta$(H) 7.67 with those at $\delta$(C) 27.7 (C(15)), 167.2 (*C*OOMe), and of the signal at $\delta$(H) 6.74 with those at $\delta$(C) 27.7 (C(15)), 195.7 (C(21)). The Me group ($\delta$(C) 14.7 (*q*), $\delta$(H) 1.98 (*d*, $J$ = 7.5)) was at C(19) ($\delta$(C) 152.6 (*d*)) according to pertinent coupling constants and HMBCs. The $^{13}$C- and DEPT-NMR spectra evidenced the presence of five downfield $sp^3$ quaternary C-atoms ($\delta$(C) 150.5, 133.6, 130.6, 127.1, 105.9), and three CH groups ($\delta$(C) 111.4, 111.0, 102.0), similar to a known 10-hydroxyindole alkaloid [8], in combination with HMBCs of $\delta$(H) 8.59 (OH) with $\delta$(C) 102.0 (C(9)), 111.4 (C(11)), and 150.5 (C(10)). The NMR spectra of **3** were similar to those of isovallesiachotamine with exception for the signals of the indole *A*-ring. Based on these findings, **3** was named 10-hydroxyisovallesiachotamine [7]. The C(19)=C(20) bond was determined as (*E*)-configured based on a ROESY correlation of $\delta$(H) 6.74 (*q*, $J$ = 7.5, H–C(19)) with $\delta$(H) 9.33 (*s*, H–C(21)). The configurations at C(3) and C(15) were deduced as (*S*) on the basis of biogenetic considerations and a ROESY correlation of $\delta$(H) 4.26 (H–C(3)) with $\delta$(H) 3.82 (H–C(15)).

Alkaloid **4** exhibited $^{13}$C-NMR signals ($\delta$(C) 137.0 (*s*, C(2)), 54.0 (*d*, C(3)), 52.1 (*t*, C(5)), 20.5 (*t*, C(6)), 106.9 (*s*, C(7)), 129.0 (*s*, C(8)), 103.1 (*d*, C(9)), 151.7 (*s*, C(10)), 111.3 (*s*, C(11)), 112.1 (*d*, C(12)), 132.2 (*s*, C(13))) and $^1$H signals ($\delta$(H) 9.46 (*s*, 1 H), 7.14 (*d*, $J$ = 8.8, 1 H), 6.83 (*d*, $J$ = 1.5, 1 H), 6.65 (*dd*, $J$ = 8.8, 1.5, 1 H)) similar to those of

Table 1. *$^{13}$C-NMR Data of* **1**–**10**. In ($D_6$)acetone; $\delta$ in ppm.

| Position | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 154.1 (*s*) | 174.4 (*s*) | 133.6 (*s*) | 137.0 (*s*) | 134.9 (*s*) | 134.6 (*s*) | 140.5 (*s*) | 139.6 (*s*) | 132.2 (*s*) | 133.8 (*s*) |
| 3 | 67.2 (*d*) | 73.2 (*d*) | 49.0 (*d*) | 54.0 (*d*) | 60.9 (*d*) | 61.2 (*d*) | 51.4 (*d*) | 51.2 (*d*) | 44.6 (*t*) | 45.5 (*t*) |
| 5 | 54.5 (*t*) | 56.8 (*t*) | 50.1 (*t*) | 52.1 (*t*) | 53.7 (*t*) | 54.5 (*t*) | 58.8 (*d*) | 58.4 (*d*) | 53.9 (*t*) | 54.9 (*t*) |
| 6 | 116.0 (*s*) | 42.4 (*t*) | 21.7 (*t*) | 20.5 (*t*) | 22.8 (*t*) | 22.1 (*t*) | 25.3 (*t*) | 25.0 (*t*) | | |
| 7 | 173.0 (*s*) | 199.2 (*s*) | 105.9 (*s*) | 106.9 (*s*) | 107.8 (*s*) | 107.2 (*s*) | 106.1 (*s*) | 106.0 (*s*) | 108.9 (*s*) | 110.0 (*s*) |
| 8 | 121.0 (*s*) | 132.0 (*s*) | 127.1 (*s*) | 129.0 (*s*) | 121.2 (*s*) | 131.8 (*s*) | 128.4 (*s*) | 127.9 (*s*) | 128.6 (*s*) | 130.0 (*s*) |
| 9 | 105.4 (*d*) | 111.2 (*d*) | 102.0 (*d*) | 103.1 (*d*) | 102.1 (*d*) | 102.0 (*d*) | 100.6 (*d*) | 118.3 (*d*) | 118.2 (*d*) | 111.9 (*d*) |
| 10 | 148.2 (*s*) | 149.0 (*s*) | 150.5 (*s*) | 151.7 (*s*) | 145.9 (*s*) | 145.9 (*s*) | 154.6 (*s*) | 119.3 (*d*) | 118.3 (*d*) | 154.3 (*s*) |
| 11 | 155.9 (*s*) | 153.4 (*s*) | 111.4 (*d*) | 111.3 (*d*) | 147.6 (*s*) | 147.5 (*s*) | 111.0 (*d*) | 121.4 (*d*) | 122.0 (*d*) | 112.8 (*d*) |
| 12 | 100.1 (*d*) | 113.8 (*d*) | 111.0 (*d*) | 112.1 (*d*) | 96.6 (*d*) | 96.6 (*d*) | 112.2 (*d*) | 111.8 (*d*) | 110.6 (*d*) | 100.7 (*d*) |
| 13 | 136.5 (*s*) | 132.3 (*s*) | 130.6 (*s*) | 132.2 (*s*) | 131.8 (*s*) | 131.2 (*s*) | 132.8 (*s*) | 137.8 (*s*) | 135.7 (*s*) | 132.0 (*s*) |
| 14 | 32.4 (*t*) | 33.0 (*t*) | 33.3 (*t*) | 33.0 (*t*) | 31.8 (*t*) | 33.5 (*t*) | 29.6 (*t*) | 29.6 (*t*) | 39.1 (*t*) | 40.8 (*t*) |
| 15 | 32.4 (*d*) | 30.4 (*d*) | 27.7 (*d*) | 33.5 (*d*) | 40.5 (*d*) | 34.8 (*d*) | 30.7 (*d*) | 30.7 (*d*) | 73.1 (*s*) | 74.4 (*s*) |
| 16 | 110.6 (*s*) | 110.7 (*s*) | 93.2 (*s*) | 52.3 (*d*) | 49.9 (*d*) | 134.8 (*s*) | 52.4 (*s*) | 51.2 (*s*) | 147.5 (*s*) | 149.0 (*s*) |
| 17 | 155.9 (*d*) | 155.6 (*d*) | 147.5 (*d*) | 63.2 (*t*) | 62.2 (*t*) | 140.8 (*d*) | 69.1 (*t*) | 76.0 (*t*) | 111.3 (*t*) | 111.1 (*t*) |
| 18 | 18.9 (*q*) | 18.3 (*q*) | 14.7 (*q*) | 13.4 (*q*) | 117.7 (*t*) | 27.1 (*t*) | 13.3 (*q*) | 13.5 (*q*) | 14.1 (*q*) | 14.4 (*q*) |
| 19 | 73.4 (*d*) | 72.5 (*d*) | 152.6 (*d*) | 122.2 (*d*) | 140.5 (*d*) | 23.1 (*t*) | 116.1 (*d*) | 117.0 (*d*) | 122.3 (*d*) | 123.2 (*d*) |
| 20 | 39.5 (*d*) | 38.6 (*d*) | 146.3 (*s*) | 136.1 (*s*) | 45.8 (*d*) | 35.1 (*d*) | 140.2 (*s*) | 139.4 (*s*) | 141.9 (*s*) | 143.0 (*s*) |
| 21 | 51.8 (*t*) | 57.0 (*t*) | 195.7 (*d*) | 57.2 (*t*) | 62.0 (*t*) | 62.1 (*t*) | 56.3 (*t*) | 56.2 (*t*) | 55.7 (*t*) | 56.6 (*t*) |
| *C*OOMe | 167.9 (*s*) | 167.6 (*s*) | 167.2 (*s*) | 175.7 (*s*) | 174.0 (*s*) | 167.5 (*s*) | 173.8 (*s*) | 173.6 (*s*) | | |
| COO*Me* | 51.3 (*q*) | 51.2 (*q*) | 50.2 (*q*) | 51.7 (*q*) | 51.4 (*q*) | 51.6 (*q*) | 51.1 (*q*) | 51.2 (*q*) | | |
| 10-MeO | 56.1 (*q*) | 56.2 (*q*) | | | 56.8 (*q*) | 56.5 (*q*) | 55.8 (*q*) | | | 55.8 (*q*) |
| 11-MeO | 56.1 (*q*) | 56.2 (*q*) | | | 56.5 (*q*) | 56.3 (*q*) | | | | |
| 1′ | | | | | | | | 104.9 (*d*) | | |
| 2′ | | | | | | | | 77.8 (*d*) | | |
| 3′ | | | | | | | | 74.9 (*d*) | | |
| 4′ | | | | | | | | 71.8 (*d*) | | |
| 5′ | | | | | | | | 77.5 (*d*) | | |
| 6′ | | | | | | | | 63.2 (*t*) | | |

Table 2. *$^1$H-NMR Data of* **1**–**5**. In ($D_6$)acetone; $\delta$ in ppm, $J$ in Hz.

| H-Atom | **1** | **2** | **3** | **4** | **5** |
|---|---|---|---|---|---|
| H–N(1) | | 9.31 (*s*) | 10.59 (*s*) | 9.46 (*s*) | 9.80 (*s*) |
| H–C(3) | 3.65 (*s*) | 2.96 (overlap) | 4.26 (*d*, *J* = 10.5) | 3.80 (*t*, *J* = 5.2) | 3.30 (*d*, *J* = 10.0) |
| $CH_2$(5) | 4.02 (*d*, *J* = 14.2), | 3.74–3.78 (*m*), | 3.88–3.92 (*m*), | 3.08–3.11 (*m*), | 3.08 (overlap), |
| | 3.50 (*d*, *J* = 14.2) | 2.69–2.71 (*m*) | 3.51–3.55 (*m*) | 2.67–2.71 (*m*) | 2.64–2.68 (*m*) |
| $CH_2$(6) | | 3.74–3.77 (*m*), | 2.69–2.72 (*m*), | 2.82–2.85 (*m*), | 2.96–3.99 (*m*), |
| | | 2.52–2.56 (*m*) | 2.58–2.61 (*m*) | 2.50–2.54 (*m*) | 2.73–2.77 (*m*) |
| H–C(9) | 7.62 (*s*) | 7.36 (*s*) | 6.69 (*s*) | 6.83 (*d*, *J* = 1.5) | 7.11 (*s*) |
| H–C(11) | | | 6.54 (*d*, *J* = 7.5) | 6.65 (*dd*, *J* = 8.8, 1.5) | |
| H–C(12) | 7.51 (*s*) | 6.84 (*s*) | 7.05 (*d*, *J* = 7.5) | 7.14 (*d*, *J* = 8.8) | 7.08 (*s*) |
| $CH_2$(14) | 2.65–2.68 (*m*), | 1.43–1.47 (*m*), | 2.26 (*d*, *J* = 13.5), | 2.20–2.23 (*m*), | 2.49 (*dt*, *J* = 12.0, 4.2), |
| | 1.52–1.54 (*m*) | 2.04 (overlap) | 1.60–1.64 (*m*) | 1.90–1.93 (*m*) | 1.47 (*q*, *J* = 12.0) |
| H–C(15) | 2.65–2.69 (*m*) | 2.52 (overlap) | 3.82 (*d*, *J* = 5.5) | 3.18–3.21 (*m*) | 1.98–2.02 (*m*) |
| H–C(16) | | | | 2.82–2.85 (*m*) | 3.04 (overlap) |
| H–C(17) | 7.05 (*s*) | 7.28 (*s*) | 7.67 (*s*) | 3.60–3.64 (*m*), | 4.10 (*dd*, *J* = 14.0, 10.0), |
| or $CH_2$(17) | | | | 3.54–3.58 (*m*) | 3.85 (*dd*, *J* = 14.0, 7.0) |
| Me(18) | 1.37 (*d*, *J* = 6.3) | 0.84 (*d*, 6.4) | 1.98 (*d*, *J* = 7.5) | 1.67 (*d*, *J* = 6.4) | 5.40 (*dd*, *J* = 17.0, 2.0), |
| or $CH_2$(18) | | | | | 5.32 (*dd*, *J* = 10.0, 2.0) |
| H–C(19) | 4.45 (br. *d*, *J* = 6.3) | 3.08 (br. *d*, 6.4) | 6.74 (*q*, *J* = 7.5) | 5.54 (*q*, *J* = 6.4) | 5.83 (*ddd*, *J* = 17.0, 13.0, 10.0) |
| H–C(20) | 1.67–1.71 (*m*) | | | | 2.58–2.62 (*m*) |
| $CH_2$(21) | 3.29 (overlap), | 2.52 (overlap), | 9.33 (*s*) | 3.67 (*d*, overlap), | 3.00 (*dd*, *J* = 11.0, 4.0), |
| or H–C(21) | 2.91 (*dd*, *J* = 3.6, 12.0) | 2.70 (*dd*, *J* = 12.0, 3.6) | | 3.06 (*d*, overlap) | 3.38 (*t*, *J* = 11.0) |
| COOMe | 3.65 (*s*) | 3.58 (*s*) | 3.49 (*s*) | | 3.79 (*s*) |
| MeO–C(10) | 3.87 (*s*) | 3.78 (*s*) | | | 3.97 (*s*) |
| MeO–C(11) | 3.85 (*s*) | 3.74 (*s*) | | | 3.95 (*s*) |

**3**, indicating both alkaloids had the same subsitition pattern in rings *A* – *C*. The HMBCs between the $CH_2$(6) H-atoms ($\delta$(H) 2.82 – 2.85 (*m*, 1 H), 2.50 – 2.54 (*m*, 1 H)) with $\delta$(C) 106.9 (C(7)), 54.0 (C(3)), and 57.2 (*t*) assigned the latter signal to C(21). Signals of both H–C(3) and H–C(21) showed HMBCs with the signal at $\delta$(C) 33.5 (*d*), attributed to C(15). The trisubstituted C=C bond ($\delta$(H) 5.54 (*q*, $J$ = 6.4, 1 H)), correlated with C(21) and C(15), confirming the presence of a C(19)=C(20) bond. A downfield MeOCO signal ($\delta$(C) 175.7 (*s*), 51.7 (*q*)) implied that the C(17), C(16) bond was saturated, which was supported by HMBCs between the signals at $\delta$(H) 3.60 – 3.64 ($H_a$–C(17)) and 3.54 – 3.58 ($H_b$–C(17)) with those at $\delta$(C) 175.7 (*s*) and 33.5 (*d*, C(15)). $^{13}$C-NMR Data of **5** for rings *A* – *C* were similar to those of reserpilline [9]. The molecular formula of **5**, $C_{21}H_{26}N_2O_4$, (HR-ESI-MS spectra) suggested a OH group at C(17). Likewise, some of its NMR pattern was also similar to those of compound **4**. Careful analysis indicated that a trisubstituted C(20)=C(19) bond in **4** changed to a terminal C(19)=C(18) bond according to the $^1$H-NMR spectrum ($\delta$(H) 5.40 (*dd*, $J$ = 17.0, 2.0, $H_a$–C(18)), 5.32 (*dd*, $J$ = 10.0, 2.0, $H_b$–C(18)), 5.83 (*ddd*, $J$ = 17.0, 10.0, 13.0, H–C(19))). Additionally, the HMBCs of the signal of H–C(19) with $\delta$(C) 40.5 (C(15)) and 62.0 (C(21)), and of that of H–C(18) with $\delta$(C) 45.8 (C(20)) confirmed this assumption. The configurations of **4** and **5** were as in sitsirikine [9], and the new compounds **4** and **5** were named 10-hydroxyisositsirikine and 10,11-dimethoxysitsirikine, respectively.

$^1$H- and $^{13}$C-NMR data of rings *A* – *C* of **6** were very similar to those signals in compound **5**. Absence of a Me(18) signal at about $\delta$(C) 13 and $\delta$(H) 1.6 ppm in $^1$H- and $^{13}$C-NMR spectra suggested that **6** was a yohimbine-type alkaloid (*Tables 1* and *3*). The signals at $\delta$(C) 167.5 (*s*), 51.6 (*q*), 134.8 (*s*), and 140.8 (*d*) indicated the presence of a COOMe group at C(16), conjugated with C(17). A MeO group was located at C(10) based on the HMBCs of the signals at $\delta$(H) 3.75 (MeO) with those at $\delta$(C) 145.9 (C(10)), and of the signal at $\delta$(H) 6.89 (H–C(12)) with those of C(10) and C(8) ($\delta$(C) 131.8). Its relative configurations at C(3), C(15), and C(20) were identical to those in **5** on the basis of the ROESY spectrum. Thus, **6** was named 10-methoxyapoyohimbine.

The $^{13}$C-NMR spectrum of **7** was very similar to that of akuammidine, except the one of the CH signals in the indole *A*-ring in akuammidine [10] was absent and replaced by a downfield quaternary C-atom signal at $\delta$(C) 154.6. This difference suggested a OH group at C(10) based on HMBCs of the signal at $\delta$(C) 6.87 (H–C(9)) with those at $\delta$(C) 106.1 (C(7)), 111.0 (C(11)), and 132.8 (C(13)), and of the signal at $\delta$(H) 6.63 (H–C(11)) with those at $\delta$(C) 100.6 (C(9)) and 132.8 (C(13)), and of the signal at $\delta$(H) 7.15 (H–C(12)) with those at $\delta$(C) 154.6 (C(10)) and 100.6 (C(9)). The $^{13}$C-NMR spectrum of **8** was also very similar to that of akuammidine except for the presence of additional sugar signals. The $J$ value (7.8 Hz) of the anomeric H-atom of the sugar moiety revealed the $\beta$-configuration of the glucopyranosyl residue. The location of the sugar unit was unambiguously determinated to be C(17) from the correlation of the H-atom signal at $\delta$(H) 4.12 (*d*, $J$ = 7.5, H–C(1′)) with that at $\delta$(C) 76.0 (*t*, C(17)) in the HMBC spectrum. So **7** and **8** were determined as 10-hydroxyakuammidine and akuammidine 17-*O*-$\beta$-D-glucopyranoside, respectively.

The UV maxima of **9** and **10** at 302 nm indicated an extended indole chromophore, same as 2-vinylindole systems as in apparicine [11]. The $^{13}$C-NMR data of **9** were very similar those of apparicine, except that the signal at $\delta$(C) 44 (*d*, C(15)) in apparicine

Table 3. *$^1$H-NMR Data of* **6**–**10**. In ($D_6$)acetone; $\delta$ in ppm, $J$ in Hz.

| H-Atom | **6** | **7** | **8** | **9** | **10** |
|---|---|---|---|---|---|
| H–N(1) | 8.90 (*s*) | 9.70 (*s*) | 9.89 (*s*) | 10.66 (*s*) | 9.76 (*s*) |
| H–C(3) | 3.19 (*d*, *J* = 10.8) | 4.17 (br. *d*, *J* = 9.6) | 4.17 (br. *d*, *J* = 9.6) | | |
| $CH_2$(5) or H–C(5) | 2.93–2.97 (*m*), 2.47–2.51 (*m*) | | 2.76–2.80 (*m*) | 4.32 (*d*, *J* = 17.6), 3.92 (*d*, *J* = 17.6) | 4.35 (*d*, *J* = 17.6), 4.00 (*d*, *J* = 17.6) |
| $CH_2$(6) | 2.80–2.84 (*m*), 2.58–2.62 (*m*) | 2.74–2.78 (*m*), 3.33–3.37 (*m*) | 2.74–2.78 (*m*), 3.33–3.37 (*m*) | | |
| H–C(9) | 6.92 (*s*) | 6.87 (*d*, *J* = 2.2) | 7.36 (*d*, *J* = 7.8) | 7.27 (*d*, *J* = 7.2) | 6.82 (*d*, *J* = 2.2) |
| H–C(10) | | | 6.94 (*d*, *J* = 7.8) | 6.89 (*t*, *J* = 7.2) | |
| H–C(11) | | 6.63 (*dd*, 7.2, 2.2) | 7.00 (*d*, *J* = 7.8) | 7.04 (*t*, *J* = 7.2) | 6.72 (*dd*, *J* = 7.2, 2.2) |
| H–C(12) | 6.89 (*s*) | 7.15 (*d*, *J* = 7.2) | 7.28 (*d*, *J* = 7.8) | 7.24 (*d*, *J* = 7.2) | 7.17 (*d*, *J* = 7.2) |
| $CH_2$(14) | 2.48 (*dt*, *J* = 12.0 3.6), 1.33 (*q*, *J* = 12.0) | 1.73–1.77 (*m*), 2.67–2.71 (*m*) | 1.74–1.77 (*m*), 2.67–2.70 (*m*) | 2.20–2.23 (*m*), 1.63–1.67 (*m*) | 2.31 (*m*), 1.80 (*m*) |
| H–C(15) | 1.79–1.83 (*m*) | 3.18 (*d*, *J* = 2.8) | 3.18 (*d*, *J* = 2.8) | | |
| H–C(17) or $CH_2$(17) | 6.95 (*t*, *J* = 3.6) | 3.81 (*d*, *J* = 11.2), 3.63 (*d*, *J* = 11.2) | 4.04 (*d*, *J* = 11.2), 3.63 (*d*, *J* = 11.2) | 5.77 (*s*), 5.70 (*s*) | 5.84 (*s*), 5.70 (*s*) |
| $CH_2$(18) | 2.28–2.31 (*m*) | 1.63 (*d*, *J* = 6.4) | 1.64 (*d*, *J* = 6.8) | 1.49 (*d*, *J* = 6.8) | 1.54 (*d*, *J* = 7.0) |
| $CH_2$(19) or H–C(19) | 1.54–1.58 (*m*), 1.98–2.02 (*m*) | 5.32 (*q*, *J* = 6.4) | 5.35 (*q*, *J* = 6.8) | 5.18 (*q*, *J* = 6.8) | 5.20 (*q*, *J* = 7.0) |
| H–C(20) | 2.77–2.81 (*m*) | | | | |
| $CH_2$(21) | 2.86–2.89 (*m*), 2.70 (*m*) | 3.50 (*d*, *J* = 11.0), 3.47 (*d*, *J* = 11.0) | 3.50 (*d*, *J* = 11.0), 3.47 (*d*, *J* = 11.0) | 3.75 (*d*, *J* = 15.0), 2.94 (*d*, *J* = 15.0) | 3.83 (*d*, *J* = 15.0), 3.00 (*d*, *J* = 15.0) |
| COOMe | 3.72 (*s*) | 2.96 (*s*) | 2.96 (*s*) | | |
| MeO–C(10) | 3.78 (*s*) | 3.76 (*s*) | | | |
| MeO–C(11) | 3.75 (*s*) | | | | |
| H–C(1′) | | | 4.12 (*d*, *J* = 7.8) | | |
| H–C(2′) | | | 3.28–3.32 (*m*) | | |
| H–C(3′) | | | 3.01–3.05 (*m*) | | |
| H–C(4′) | | | 3.25–3.29 (*m*) | | |
| H–C(5′) | | | 3.27–3.31 (*m*) | | |
| $CH_2$(6′) | | | 2.82 (br. *d*, *J* = 10.0), 3.65 (br. *d*, *J* = 10.0) | | |

was substituted by that at $\delta$(C) 73.1 in **9**, indicating that the OH group at C(15) in **9** adopted the $\alpha$-orientation. The molecular formula of alkaloid **10**, $C_{19}H_{22}N_2O_2$, according to HR-ESI-MS was 30 amu higher than that of **9**, indicating that this new alkaloid possesses an additional MeO group. In the $^1$H-NMR spectrum of **10**, three H-atom signals ($\delta$(H) 6.82 (*d*, *J* = 2.2, H–C(9)), 6.72 (*dd*, *J* = 7.2, 2.2, H–C(11)), and 7.17 (*d*, *J* = 7.2, H–C(12))) evidenced presence of 10-methoxyindole moiety. So **9** and **10** were named 15$\alpha$-hydroxyapparicine and 15$\alpha$-hydroxy-10-methoxyapparicine, respectively.

The remaining alkaloids were identified by comparison of their NMR spectroscopic data with those in the literature. All alkaloids were evaluated for their cytotoxicities against five human cancer cell lines. Only **3**, ellipticine, and 10-methoxyellipticine exhibited cytotoxicities against HL-60, SMMC-7721, A-549, MCF-7, and SW-480 cells (*Table 4*).

Table 4. *Cytotoxicity* ($IC_{50}$ [μM]) *of Alkaloids*

| Alkaloids | HL-60 | SMMC-7721 | A-549 | MCF-7 | SW-480 |
|---|---|---|---|---|---|
| **3** | 3.10 | 6.70 | 15.23 | 6.28 | 8.92 |
| Ellipticine | 0.46 | 2.39 | 1.10 | 2.11 | 1.97 |
| 10-Methoxyellipticine | 0.08 | 0.70 | 0.27 | 0.63 | 2.24 |
| DDP (MW300) | 1.14 | 14.51 | 12.76 | 17.18 | 16.84 |

## Experimental Part

*General*. Column chromatography (CC): silica gel ($SiO_2$; 200–300 mesh, *Qingdao Haiyang Chemical Co., Ltd.*, Qingdao, China) and $C_{18}$ $SiO_2$ (20–45 μm, *Fuji Silysia Chemical Ltd.*), monitoring by TLC on $SiO_2$ plates ($GF_{254}$, *Qingdao Haiyang Chemical Co., Ltd.*), and visualization of the spots by spraying with *Dragendorff*'s reagent. Medium-pressure liquid chromatography (MPLC): *Büchi* pump system coupled with a $C_{18}$-$SiO_2$-packed glass column (15 × 230 and 26 × 460 mm, resp.). HPLC: *Waters 1525EF* pump (*Waters Corp.*, Milford, MA, USA) coupled with a *Sunfire* anal. semi-prep., or prep. $C_{18}$ column (150 × 4.6, 150 × 10 mm, and 250 × 19 mm, resp.); *Waters 2998* photodiode array detector and *Waters fraction collector III* (*Waters Corp.*). Optical rotations: *Horiba SEPA-300* polarimeter (*Horiba Scientific*, Kyoto, Japan) or *JASCO DIP-370* digital polarimeter (*Jasco International Co.*, Tokyo, Japan). UV Spectra: *Shimadzu UV-2401A* spectrophotometer (*Shimadzu Corp.*, Kyoto, Japan) in MeOH; $\lambda_{max}$ (log $\varepsilon$) in nm. IR Spectra: *Tenor 27* spectrophotometer using KBr pellets; $\tilde{\nu}$ in $cm^{-1}$. 1D- and 2D-NMR spectra: *Bruker Avance III-600*, *DRX-500*, and *AM-400* spectrometers (*Bruker BioSpin GmBH*, Rheinstetten, Germany); $\delta$ in ppm rel. to $Me_4Si$ as internal standard, *J* in Hz. ESI- and HR-ESI-MS: *API QSTAR Pulsar 1* spectrometer (*Applied Biosystems, Ltd.*, Warrington, UK); in *m*/*z*.

*Plant Material.* Leaves and twigs of *O. borbonica* J.F.GMEL. were collected in February, 2011, in Guangzhou, Guangdong Province, P. R. China, and identified by Prof. *Hua-Gu Ye*, South China Botanical Garden, Chinese Academy of Sciences. A voucher specimen (Cai110206) was deposited with the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

*Extraction and Isolation.* After being dried and powdered, 9 kg of *O. borbonica* leaves and twigs were extracted three times with MeOH at r.t., and the solvent was removed *in vacuo*. The residue was dissolved in 0.3% aq. HCl (*v*/*v*) and partitioned with AcOEt. The aq. layer was basified with aq. $NH_3$ to pH 9–10, and partitioned with AcOEt. The AcOEt layer (98 g) was subjected to CC ($SiO_2$ (1.0 kg); $CHCl_3$/acetone from 1:0 to 1:1) to afford seven fractions, *Frs. I–VII*. *Fr. I* (10 g) was further purified on a prep. $C_{18}$ MPLC column with a gradient flow of 70, 77, and 85% aq. MeOH to yield reserpiline (7 mg),

isoreserpiline pseudoindoxyl (11 mg), and **2** (6 mg). *Fr. II* (9 g) was further chromatographed on $C_{18}$ $SiO_2$ with a gradient flow of 70, 75, and 80% aq. MeOH to yield epchrosine (11 mg), **8** (19 mg), and 11-methoxyapoyohimbine (10 mg). *Fr. III* (5.2 g) was purified on a $C_{18}$ MPLC column with a MeOH/$H_2O$ gradient eluent (6:4–8:2) to yield subfraction *III-1*. 10,11-Dimethoxypicraphylline (14 mg), 10-methoxyellipticine (355 mg), and ellipticine (420 mg), resp., were obtained from *III-1* on a prep. $C_{18}$ HPLC column with a gradient flow of 65–73% aq. MeOH. *Fr. IV* (12 g) was purified by $C_{18}$ MPLC column with a MeOH/$H_2O$ gradient (1:1–4:1) to yield subfractions, *Frs. IV-1–IV-4*. *Fr. IV-1* (124 mg) was further separated on a semi-prep. $C_{18}$ HPLC column with 50% aq. MeOH to yield epchrosine (7 mg) and apparicine (20 mg). 10-Methoxyellipticine (56 mg) was crystallized from *Fr. IV-2*. *Fr. IV-3* (74 mg) was further separated on the same column with a gradient flow of 55–65% aq. MeOH to yield 10-methoxyellipticine (7 mg), **5** (5 mg), begonanline (6 mg), and **6** (9 mg). *Fr. IV-4* (74 mg) was further separated on the same column with a gradient flow of 55–65% aq. MeOH to yield akuammidine (17 mg), 11-methoxypseudoyohime (21 mg), and **3** (8 mg). *Fr. V* (11 g) was purified on a $C_{18}$ MPLC column with a MeOH/$H_2O$ gradient eluent (1:1–4:1) to yield subfractions *Frs. V-1–V-3*. *Fr. V-1* (474 mg) was further separated on a prep. $C_{18}$ HPLC column with a gradient flow of 50–60% aq. MeOH to afford **7** (19 mg) and **1** (5 mg). 10-Methoxyapparicine (21 mg) was crystallized from *Fr. V-2*. Its mother liquid (121 mg) was further separated on a $C_{18}$ prep. column with a gradient flow of 55–65% aq. MeOH to give 10-methoxyapparicine (5 mg), 11-methoxy-$\beta$-yohimbine (6 mg), and hervine (16 mg). *Fr. IV-3* (190 mg) was further separated on a prep. $C_{18}$ column with a gradient flow of 57–67% aq. MeOH to afford 16-epiisositsirikine (13 mg) and 16-epipleiocarpamine (11 mg). *Fr. VI* (9 g) was purified on $C_{18}$ column with a MeOH/$H_2O$ gradient eluent (1:1–7:3) to yield subfractions, *Frs. VI-1–VI-3*. *Fr. VI-1* (160 mg) was further separated on a prep. $C_{18}$ column with a gradient flow of 40–55% aq. MeOH to afford (16*R*)-10-methoxyisositsirikine (19 mg) and (16*S*)-10-methoxyisositsirikine (26 mg). *Fr. VI-2* (130 mg) was further separated on a prep. $C_{18}$ column with a gradient flow of 50–60% aq. MeOH to give **4** (11 mg), **5** (6 mg), and carapanaubine (7 mg). *Fr. VI-3* (135 mg) was further separated on a prep. $C_{18}$ HPLC column with a gradient flow of 50–60% aq. MeOH to afford 3-epicarapanaubine (7 mg) and **10** (9 mg). *Fr. VII* (7 g) was purified by CC ($SiO_2$; $CHCl_3$/MeOH 9:1–4:1) to yield subfractions, *Frs. VII-1–VII-2*. *Fr. VII-1* (190 mg) was further separated on a prep. $C_{18}$ column with a gradient flow of 45–60% aq. MeOH to afford cabucine (9 mg), ochropposine (14 mg), and isovallesiachotamine (4 mg). Alkaloid **9** (6 mg) and 18,19-dihydro-10-methoxysitsirikine (11 mg) were separated on a prep. $C_{18}$ HPLC column with a gradient flow of 50–55% aq. MeOH from *Fr. VII-2*.

*Ochroborine A* (= *Methyl (1*S*,4a*S*,5a*S*,14a*R*)-4a,5,5a,6,11,12,14,14a-Octahydro-8,9-dimethoxy-1-methyl-11-oxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-4-carboxylate*; **1**). White powder. $[\alpha]_D^{20} = -246$ ($c = 0.12$, MeOH). UV (MeOH): 232 (3.42), 292 (3.14). IR (KBr): 3433, 2923, 1705, 1623, 1598. $^1$H- and $^{13}$C-NMR: see *Tables 2* and *1*, resp. ESI-MS (pos.): 427 (100, $[M+H]^+$). HR-ESI-MS: 427.1870 ($[M+H]^+$, $C_{23}H_{27}N_2O_6^+$; calc. 427.1869).

*Ochroborine B* (= *Methyl (1*S*,4a*S*,5a*S*,16a*R*)-4a,5,5a,6,7,12,13,14,16,16a-Decahydro-9,10-dimethoxy-1-methyl-6,12-dioxo-1*H*-pyrano[4′,3′:4,5]pyrido[2,1-*c*][1,4]benzodiazonine-4-carboxylate*; **2**). White powder. $[\alpha]_D^{20} = -27$ ($c = 0.12$, MeOH). UV (MeOH): 238 (3.89), 290 (3.05). IR (KBr): 3446, 2921, 1678, 1644, 1601, 1461. $^1$H- and $^{13}$C-NMR: see *Tables 2* and *1*, resp. ESI-MS (pos.): 445 ($[M+H]^+$). HR-ESI-MS: 467.1794 ($[M+Na]^+$, $C_{23}H_{28}N_2NaO_7^+$; calc. 467.1794).

*10-Hydroxyisovallesiachotamine* (= *Methyl (2*S*,12b*S*)-1,2,6,7,12,12b-Hexahydro-9-hydroxy-2-[(2*E*)-1-oxobut-2-en-2-yl]indolo[2,3-*a*]quinolizine-3-carboxylate*; **3**). White powder. $[\alpha]_D^{20} = -71$ ($c = 0.16$, MeOH). UV (MeOH): 229 (4.25), 282 (3.90), 292 (3.52). IR (KBr): 3432, 2924, 1722, 1628, 1600, 1462. $^1$H- and $^{13}$C-NMR: see *Tables 2* and *1*, resp. ESI-MS (pos.): 367 ($[M+H]^+$). HR-ESI-MS: 367.1660 ($[M+H]^+$, $C_{21}H_{23}N_2O_4^+$; calc. 367.1658).

*10-Hydroxyisositsirikine* (= *Methyl (2*R*)-2-[(2*R*,3*E*,12b*S*)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydro-9-hydroxyindolo[2,3-*a*]quinolizin-2-yl]-3-hydroxypropanoate*; **4**). White powder. $[\alpha]_D^{20} = -62$ ($c = 0.09$, MeOH). UV (MeOH): 224 (3.95), 282 (3.27). IR (KBr): 3483, 2924, 1686, 1668, 1598. $^1$H- and $^{13}$C-NMR: see *Tables 2* and *1*, resp. ESI-MS (pos.): 371 ($[M+H]^+$). HR-ESI-MS: 371.1970 ($[M+H]^+$, $C_{21}H_{27}N_2O_4^+$; calc. 371.1971).

*10,11-Dimethoxysitsirikine* (= *Methyl (2*R*)-2-[(2*S*,3*R*,12b*S*)-3-Ethenyl-1,2,3,4,6,7,12,12b-octahydro-9,10-dimethoxyindolo[2,3-*a*]quinolizin-2-yl]-3-hydroxypropanoate*; **5**). White powder. $[\alpha]_D^{20} = -53$ ($c =$

0.12, MeOH). UV (MeOH): 228 (4.11), 283 (3.93). IR (KBr): 3443, 2912, 1651, 1602. $^1$H- and $^{13}$C-NMR: see *Tables 2* and *1*, resp. ESI-MS (pos.): 415 ($[M+H]^+$). HR-ESI-MS: 415.2120 ($[M+H]^+$, $C_{23}H_{31}N_2O_5^+$; calc. 415.2123).

*10-Methoxyapoyohimbine* (= *Methyl 16,17-Didehydro-10,11-dimethoxyyohimban-16-carboxylate*; **6**). White powder. $[\alpha]_D^{20} = 92$ ($c = 0.11$, MeOH). UV (MeOH): 224 (3.99), 290 (3.50). IR (KBr): 3443, 2923, 1716, 1651, 1602. $^1$H- and $^{13}$C-NMR: see *Tables 3* and *1*, resp. ESI-MS (pos.): 397 ($[M+H]^+$). HR-ESI-MS: 397.2123 ($[M+H]^+$, $C_{23}H_{29}N_2O_4^+$; calc. 397.2127).

*10-Hydroxyakuammidine* (= *Methyl (19*E*)-10,17-Dihydroxysarpagan-16-carboxylate*; **7**). White powder. $[\alpha]_D^{20} = -47$ ($c = 0.13$, MeOH). UV (MeOH): 223 (3.91), 281 (3.38). IR (KBr): 3340, 2923, 1711, 1653, 1602. $^1$H- and $^{13}$C-NMR: see *Tables 3* and *1*, resp. ESI-MS (pos.): 369 ($[M+H]^+$). HR-ESI-MS: 369.1818 ($[M+H]^+$, $C_{21}H_{25}N_2O_4^+$; calc. 369.1814).

*Akuammidine 17-*O*-β-*D*-Glucopyranoside* (= *Methyl (19*E*)-17-(β-*D*-Glucopyranosyloxy)-10-hydroxysarpagan-16-carboxylate*; **8**). White powder. $[\alpha]_D^{20} = -153$ ($c = 0.12$, MeOH). UV (MeOH): 227 (3.81), 282 (3.38). IR (KBr): 3447, 2922, 1712, 1650, 1602. $^1$H- and $^{13}$C-NMR: see *Tables 3* and *1*, resp. ESI-MS (pos.): 515 ($[M+H]^+$). HR-ESI-MS: 315.2395 ($[M+H]^+$, $C_{27}H_{35}N_2O_8^+$; calc. 514.2393).

*15α-Hydroxyapparicine* (= *(4Z,5*R*)-4-Ethylidene-3,4,6,7-tetrahydro-6-methylidene-2,5-ethanoazocino[4,3-*b*]indol-5(1*H*)-ol*; **9**). White powder. $[\alpha]_D^{20} = +189$ ($c = 0.12$, MeOH). UV (MeOH): 227 (3.91), 281 (3.37). IR (KBr): 3453, 2922, 1710, 1650, 1601. $^1$H- and $^{13}$C-NMR: see *Tables 3* and *1*. ESI-MS (pos.): 281 ($[M+H]^+$). HR-ESI-MS: 281.1651 ($[M+H]^+$, $C_{18}H_{21}N_2O^+$; calc. 281.1654).

*15α-Hydroxy-10-methoxyapparicine* (= *(4Z,5*R*)-4-Ethylidene-3,4,6,7-tetrahydro-10-methoxy-6-methylidene-2,5-ethanoazocino[4,3-*b*]indol-5(1*H*)-ol*; **10**). White powder. $[\alpha]_D^{20} = +172$ ($c = 0.14$, MeOH). UV (MeOH): 227 (3.98), 283 (3.51). IR (KBr): 3513, 2923, 1660, 1602. $^1$H- and $^{13}$C-NMR: see *Tables 3* and *1*, resp. ESI-MS (pos.): 311 ($[M+H]^+$). HR-ESI-MS: 311.1762 ($[M+H]^+$, $C_{19}H_{23}N_2O_2^+$; calc. 311.1760).

*Cytotoxicity Assay.* Five human cancer cell lines, MCF-7 breast, SMMC-7721 hepatocellular carcinoma, HL-60 myeloid leukemia, SW480 colon cancer, and A-549 lung cancer, were used for cytotoxic assays. Cells were cultured in RPMI-1640 (*Sigma–Aldrich*, St. Louis, MO, USA) or in a DMEM medium (*Hyclone*, Logan, UT, USA), supplemented with 10% fetal bovine serum (*Hyclone*) in 5% $CO_2$ at 37°. Cytotoxicity assays were performed according to the MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) method in 96-well microplates. Briefly, 100 µl of adherent cell types were seeded into each well of 96-well cell culture plates and allowed to adhere for 12 h before the addition of test compounds. Suspended cell types were seeded with an initial density of $1 \times 10^5$ cells/ml just before drug addition. Each tumor cell line was exposed to a test compound at concentrations of 0.039, 0.201, 1.005, 5.024, and 25.120 µg/ml in triplicate for 48 h, with cisplatin (*Sigma–Aldrich*) as the positive control (*Table 4*). After treatment, cell viability was assessed, cell growth was graphed, and $IC_{50}$ values were calculated by *Reed* and *Muench*'s method.

This work was financially supported by the *National Natural Science Foundation of China* (21172225), the *Young Academic and Technical Leader Raising Foundation of Yunnan Province* (No. 2010CI049), and the *Chinese Academy of Sciences* (*XiBuZhiGuang Project*).

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*Received March 24, 2013*